



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Randomized controlled trial of dual antiplatelet therapy in patients undergoing surgery for critical limb ischemia

Citation for published version:

Burdess, A, Nimmo, AF, Garden, OJ, Murie, JA, Dawson, ARW, Fox, KAA & Newby, DE 2010, 'Randomized controlled trial of dual antiplatelet therapy in patients undergoing surgery for critical limb ischemia', *Annals of Surgery*, vol. 252, no. 1, pp. 37-42. <https://doi.org/10.1097/SLA.0b013e3181e40dde>

Digital Object Identifier (DOI):

[10.1097/SLA.0b013e3181e40dde](https://doi.org/10.1097/SLA.0b013e3181e40dde)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Early version, also known as pre-print

Published In:

Annals of Surgery

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Randomized Controlled Trial of Dual Antiplatelet Therapy in Patients Undergoing Surgery for Critical Limb Ischemia

Anne Burdess, MB, ChB,* Alastair F. Nimmo, MD,† O. James Garden, MD,* John A. Murie, MD,‡
A. Raymond W. Dawson, MD,‡ Keith A. A. Fox, BSc (Hons), MB ChB, FRCP, FESC, FMed Sci,§
and David E. Newby, PhD§

Background and Objective: Patients with critical limb ischemia have a perioperative cardiovascular morbidity comparable to patients with acute coronary syndromes. We hypothesized that perioperative dual antiplatelet therapy would improve biomarkers of atherothrombosis without causing unacceptable bleeding in patients undergoing surgery for critical limb ischemia.

Methods: In a double-blind randomized controlled trial, 108 patients undergoing infrainguinal revascularization or amputation for critical limb ischemia were maintained on aspirin (75 mg daily) and randomized to clopidogrel (600 mg prior to surgery, and 75 mg daily for 3 days; n = 50) or matched placebo (n = 58). Platelet activation and myocardial injury were assessed by flow cytometry and plasma troponin concentrations, respectively.

Results: Clopidogrel reduced platelet-monocyte aggregation before surgery (38%–30%; $P = 0.007$). This was sustained in the postoperative period ($P = 0.0019$). There were 18 troponin-positive events (8 [16.0%] clopidogrel vs. 10 [17.2%] placebo; relative risk [RR]: 0.93, 95% confidence interval [CI]: 0.39–2.17; $P = 0.86$). Half of troponin-positive events occurred preoperatively with clopidogrel causing a greater decline in troponin concentrations ($P < 0.001$). There was no increase in major life-threatening bleeding (7 [14%] vs. 6 [10%]; RR: 1.4, 95% CI: 0.49–3.76; $P = 0.56$) or minor bleeding (17 [34%] vs. 12 [21%]; RR 1.64, 95% CI: 0.87–3.1; $P = 0.12$), although blood transfusions were increased (28% vs. 12.6%, RR: 2.3, 95% CI: 1.0–5.29; $P = 0.037$).

Conclusions: In patients with critical limb ischemia, perioperative dual antiplatelet therapy reduces biomarkers of atherothrombosis without causing unacceptable bleeding. Large-scale randomized controlled trials are needed to establish whether dual antiplatelet therapy improves clinical outcome in high-risk patients undergoing vascular surgery.

(*Ann Surg* 2010;252: 37–42)

From the Departments of *Clinical and Surgical Sciences, and †Anaesthesiology, The University of Edinburgh, Edinburgh, United Kingdom; ‡Department of Vascular Surgery, The Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; and §Centre for Cardiovascular Science, The University of Edinburgh, Edinburgh, United Kingdom.

Supported by grants from the British Heart Foundation (FS/05/038); European Society of Vascular Surgery Research Awards; Royal College of Surgeons of Edinburgh Research Grants and an unrestricted educational award from Sanofi Aventis.

This study was registered on the ISRCT and EUDRA websites. International Standardised RCT: ISRCTN22305120. Weblink: <http://www.controlled-trials.com/ISRCTN22305120>.

Trial start date: June 1, 2005. Eudract Number: 2005–000960–25. CTA Number: 11449/0002/001–0001 (Granted 05/04/05). REC reference number: 05/S0501/41 (Granted 29/04/05).

There was no involvement of Sanofi Aventis in any aspect of the trial including protocol design, study conduct or data analysis.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

Reprints: Anne Burdess, MB, ChB, Department of Clinical and Surgical Sciences, The University of Edinburgh, Room SU304, The Chancellor's Building, 49 Little France Crescent, Edinburgh, EH16 4SB, United Kingdom. E-mail: anne.burdess@ed.ac.uk.

Copyright © 2010 by Lippincott Williams & Wilkins

ISSN: 0003-4932/10/25201-0037

DOI: 10.1097/SLA.0b013e3181e40dde

Patients with peripheral arterial disease have an increased risk of adverse cardiovascular events,¹ particularly in the perioperative period.² Myocardial injury is the commonest life-threatening complication of vascular surgery with a reported incidence ranging from 8% to 40%.^{3–5} This is comparable to the cardiovascular risk of patients presenting with an acute coronary syndrome: 30-day death and reinfarction rate of 8% to 20%.⁶

In patients with peripheral arterial disease, prophylactic use of the thienopyridine clopidogrel has modest additional secondary preventative benefits in comparison to,⁷ or in combination with,⁸ aspirin. Combination aspirin and clopidogrel therapy is of major benefit in reducing recurrent ischemic events in patients with acute coronary syndromes.⁹ It is therefore reasonable to postulate that dual antiplatelet therapy may have particular benefits in patients undergoing vascular surgery. However, many clinicians would question the wisdom of dual antiplatelet therapy in the operative setting because of the risk of increased peri-operative bleeding. The CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial reported an overall relative risk reduction in cardiovascular death, myocardial infarction, or stroke in patients undergoing coronary artery bypass grafting following non-ST segment elevation myocardial infarction, without an increase in major life-threatening bleeding.¹⁰ However, the surgical subgroup was not prospectively randomized and only a small proportion of patients received dual antiplatelet therapy within 5 days of operation. Despite these limitations, the trial proposed that the potential cardiovascular benefits of dual antiplatelet therapy may outweigh the risks of bleeding in the high-risk surgical patient.

Atherothrombosis is the major underlying cause of adverse cardiovascular events. Platelets play a key role in this process and are associated with both the inflammatory destabilization of atherosclerotic plaques, and thrombus generation.^{11,12} Platelet activation is commonly assessed using aggregometry or detection of platelet surface P-selectin expression following ex vivo agonist stimulation. These approaches are artificial and may not truly reflect the status of in vivo platelet activation because of the potential for in vitro activation, and the rapid shedding of P-selectin from the platelet surface.¹³ Activated platelets are rapidly cleared from the circulation by monocytes and the quantification of platelet-monocyte aggregates is now emerging as the “gold standard” assessment for in vivo platelet activation.^{14,15} We and others have demonstrated that platelet-monocyte aggregates are increased in those who smoke or have diabetes mellitus as well as in patients with peripheral arterial disease or an acute coronary syndrome.^{16–19}

To date, there have been no studies to investigate the effects of dual antiplatelet therapy in patients undergoing surgery for critical limb ischemia. Given the potential for both marked benefit and hazard, we embarked upon a proof-of-concept pilot randomized controlled trial. We hypothesized that combined perioperative aspirin and clopidogrel therapy would improve biomarkers of atherothrombosis (platelet-monocyte aggregates and troponin release) without causing unacceptable bleeding, in patients undergoing surgery for critical limb ischemia.

METHODS

Subjects

Patients with critical limb ischemia who were scheduled for infra-inguinal bypass, femoral endarterectomy or lower limb amputation under general anesthesia were recruited into the study. Critical limb ischemia was defined as the presence of rest pain or skin breakdown, resulting from arterial disease. Exclusion criteria included women of child bearing potential, nonatherosclerotic vascular disease, sudden acute limb ischemia requiring emergency surgery, supra-inguinal or aortic surgery, history of acute coronary syndrome within 3 months, history of peptic ulcer disease, previous or current intracranial hemorrhage, bleeding diathesis, uncontrolled hypertension, or thrombocytopenia, planned epidural or spinal anesthesia, hypersensitivity or allergy to thienopyridines, and current warfarin or thienopyridine use.

Study Design

Patients were recruited between June 2005 and February 2008, and gave written informed consent prior to study participation. The study was approved by the local Research Ethics Committee, given Clinical Trial Authorization by the Medicines and Healthcare products Regulatory Agency (United Kingdom), and was conducted in accordance with the Declaration of Helsinki and CONSORT guidelines.^{20,21}

This was a prospective single center double-blind randomized controlled trial at a tertiary referral vascular surgical unit in the Royal Infirmary of Edinburgh, South-East Scotland, United Kingdom.

Treatment Allocation

Following recruitment, clopidogrel and matched placebo were assigned in identical packs by the pharmacy trials unit through allocation of sequentially numbered study medication packs that had been randomized using an independent computer-generated sequence. Patients received 600 mg of clopidogrel or matched placebo 4 to 28 hours prior to surgery and received 75 mg of clopidogrel or matched placebo daily for 3 days after surgery (Studies suggest that the incidence of peri-operative adverse cardiovascular events is greatest within the first 5 days of surgery.² We therefore commenced therapy preoperatively and continued maintenance levels into a short postoperative period.). Patients undergoing bypass procedures received a single dose of 5000 IU of intravenous unfractionated heparin during surgery before arterial clamping. At the discretion of the clinical team, intravenous protamine was given only if excessive bleeding was felt to be present at the end of the operation. All patients received subcutaneous unfractionated heparin 5000 IU twice daily in the postoperative period and were maintained on aspirin (75 mg daily) throughout the study.

Biomarkers of Atherothrombosis

Platelet Activation and Inflammatory Markers

Blood samples were taken before, and a minimum of 4 hours after, a loading dose of 600 mg of clopidogrel or matched placebo, immediately after the operation in the recovery room, and on day 1 after surgery. Flow cytometric measurements of platelet-monocyte aggregates and platelet surface expression of P-selectin were used as markers of in vivo platelet activation as described previously.^{16,17,19,22} Directly conjugated monoclonal antibodies were obtained from DakoCytomation (Cambridge, United Kingdom) and Serotec (Oxford, United Kingdom).

Myocardial Injury

The Reference Clinical Biochemistry Laboratory measured plasma troponin I concentrations using the ARCHITECT Troponin I STAT assay (Abbott Diagnostics, Maidenhead, United Kingdom)

using an autoanalyzer. This has an analytical sensitivity of 0.009 ng/mL and a functional sensitivity of 0.032 ng/mL with a coefficient of variation of <10%. The latter threshold was employed for the clinical case definition of myocardial infarction (see below).

In-Patient Clinical Outcomes

Acute Coronary Syndromes

Clinical symptoms, plasma troponin concentrations and electrocardiograms were recorded daily from the preoperative day until day 3 postsurgery. A blinded independent cardiologist reviewed all clinical data and applied the universal definition of myocardial infarction.²³

Bleeding Complications

Bleeding events were defined as major (life-threatening or nonlife threatening) and minor according to CURE criteria.¹⁰ Postoperative blood transfusions were recommended according to Scottish Intercollegiate Guidelines Network (SIGN) criteria.²⁴ Intraoperative blood loss, postoperative fall in hemoglobin, blood product transfusion, length of operation and length of hospital stay were recorded. Incidence of gastro-intestinal bleeding, persistent (>3 days) wound leak, hematoma, or infection were documented.

Data and Statistical Analysis

An independent data monitoring committee performed an interim safety analysis of bleeding outcomes following recruitment of 50 patients and recommended continuation of the trial to completion. Following completion of trial recruitment, data collection, and laboratory analyses, the data base was locked, treatment allocation unblinded and prespecified analyses performed. The primary end-point was platelet-monocyte aggregation. The sample size ($n = 50$ per group) was based on our previous studies^{16,17,19} and gave an 80% power of detecting a 4.8% difference in platelet-monocyte aggregates at a significance level of 5%. Secondary outcomes included plasma troponin concentration, and rate of myocardial infarction and bleeding complications. Continuous variables are reported as mean \pm SD. Analysis of variance with repeated measures, 2-tailed Student t test and χ^2 analysis were performed as appropriate using GraphPad Prism Version 4 (La Jolla, US). Statistical significance was taken as a 2-sided P value <0.05.

Statement of Responsibility

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Of the 159 potentially eligible patients, 113 were randomized to trial medication (Fig. 1). Of those who completed the study protocol, 58 received placebo and 50 received clopidogrel. There was no difference in baseline demographics between the 2 groups (Table 1; Appendix 1, Supplemental Digital Content 1, online only, available at: <http://links.lww.com/SLA/A53>).

Biomarkers of Atherothrombosis

Platelet Activation

In keeping with the patient population, baseline levels of platelet-monocyte aggregation were markedly elevated. There was no difference in baseline platelet-monocyte aggregates ($P = 0.80$) and P-selectin expression ($P = 0.80$) between the 2 groups. Platelet activation was unaffected by placebo ($P = 0.78$) but clopidogrel (600 mg) caused a rapid reduction in platelet-monocyte aggregates ($38\% \pm 17\%$ – $30\% \pm 17\%$, $P = 0.007$) and platelet P-selectin expression ($4.9\% \pm 2.7\%$ – $2.8\% \pm 1.6\%$, $P < 0.0001$). In both

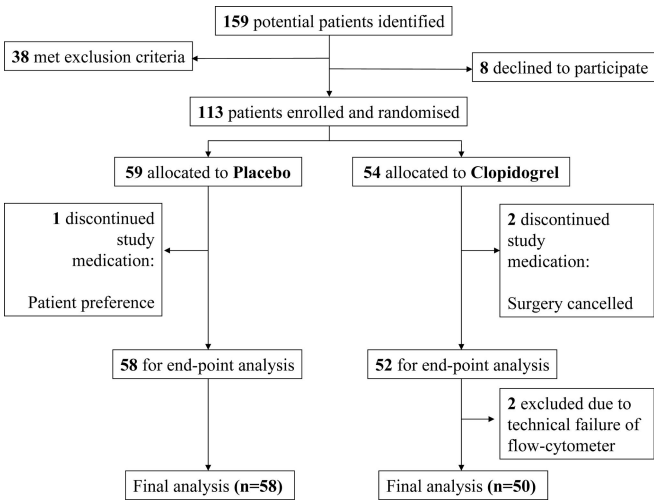


FIGURE 1. Trial profile.

TABLE 1. Baseline Characteristics of Patients According to Interventional Group

Variable	Clopidogrel n = 50	Placebo n = 58	P
Age (yr)	68 ± 2	68 ± 2	0.83
Male sex	39 (78)	45 (78)	0.96
Critical limb ischemia			
Ankle-brachial pressure index <0.2	34 (68)	31 (53)	0.12
Skin changes (ulcer/gangrene)	27 (54)	34 (59)	0.63
Rest pain	42 (84)	49 (84)	1.00
Operation			
Bypass	32	41	0.71
Amputation	14	14	0.71
Combined bypass and angioplasty	4	3	0.71
Lees revised cardiac risk index ≥3 ²⁵	40	43	0.47
Cardiac risk factors			
Diabetes mellitus	19 (38)	19 (33)	0.57
Hypertension	41 (82)	48 (83)	0.91
Hypercholesterolemia	31 (62)	37 (64)	0.85
Family history of ischemic heart disease	5 (11)	8 (14)	0.55
Current smoker	20 (40)	31 (53)	0.36
Serum creatinine (μmol/L)	98 ± 4	106 ± 6	0.27
Ischemic heart disease	20 (40)	31 (56)	0.16
Cerebrovascular disease	11 (22)	15 (26)	0.64
Drugs			
Aspirin	50 (100)	58 (100)	1.00
Statin	35 (70)	45 (78)	0.37
Beta-blockade	13 (26)	12 (21)	0.43
Angiotensin-converting enzyme inhibition	19 (38)	24 (41)	0.72

Variables reported as mean ± SD or n (%) and analyzed with unpaired *t* test or χ^2 analysis as appropriate.

groups, platelet activation declined within 24 hours of surgery ($P \leq 0.005$), but clopidogrel treatment was associated with greater reductions throughout the immediate postoperative period ($P = 0.0019$; Fig. 2). To assess pharmacological efficacy of the trial intervention,

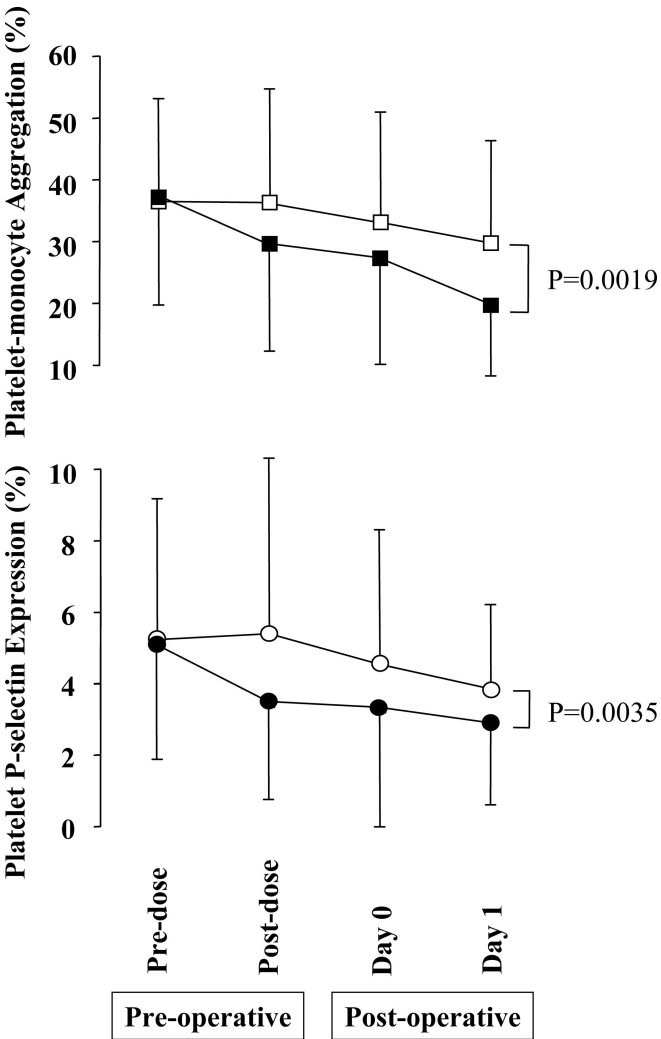


FIGURE 2. Platelet-monocyte aggregates (squares; $P < 0.0001$ for both groups) and platelet P-selectin expression (circles; $P \leq 0.005$ for both groups) over the perioperative period in patients receiving placebo or clopidogrel. Clopidogrel (closed symbols) caused a greater reduction in both platelet-monocyte aggregates ($P = 0.0019$) and platelet P-selectin expression ($P = 0.0035$) compared with placebo (open symbols). Symbols represent mean ± SD; analysis by 2-way ANOVA.

ex vivo platelet aggregation to 5 μ M adenosine diphosphate was performed in a subgroup of trial participants ($n = 10$ per group). This confirmed that clopidogrel inhibited adenosine diphosphate-induced aggregation ($59\% \pm 20\%$ – $33\% \pm 18\%$, $P < 0.0001$) throughout the perioperative period ($P = 0.0015$; data not shown).

Myocardial Injury

Of the 108 trial subjects, 18 (16.7%) suffered an elevated plasma troponin concentration (>0.032 ng/mL): 8 (16.0%) received clopidogrel and 10 (17.2%) placebo (relative risk [RR] 0.93, 95% confidence intervals [CI] 0.40–2.17; $P = 0.86$). Nine (8.3%) patients (4 clopidogrel and 5 placebo) had an elevation of plasma troponin concentration before surgery, and 9 patients (4 clopidogrel and 5 placebo) suffered a postoperative rise in troponin. Of those 9

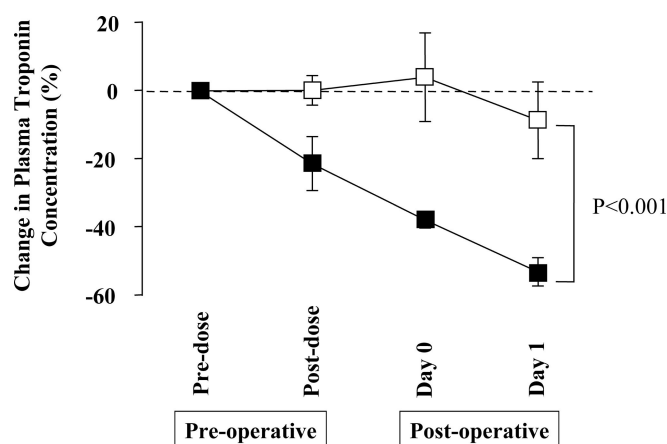


FIGURE 3. Change in plasma troponin concentrations in patients with preoperative troponin elevations on placebo (open squares) or clopidogrel (closed squares). Symbols represent mean \pm SD, $P < 0.001$; 2-way ANOVA, clopidogrel ($n = 4$) versus placebo ($n = 5$).

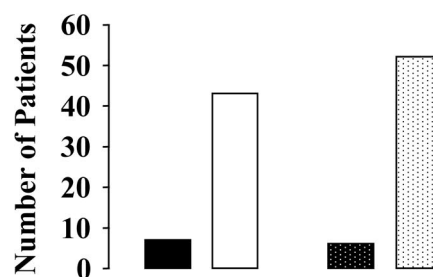
patients who sustained a preoperative troponin rise, plasma troponin concentrations fell with clopidogrel therapy but remained unchanged or increased in those on placebo (Fig. 3). Patients with postoperative elevation in plasma troponin concentrations had greater platelet-monocyte aggregates ($40\% \pm 4\%$ vs. $30\% \pm 2\%$; $P = 0.033$).

Clinical Outcomes

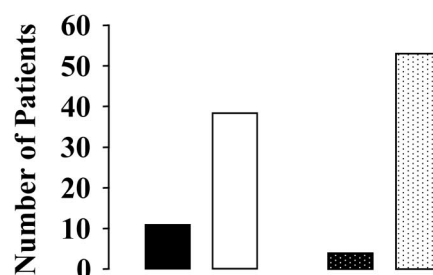
Of the 108 trial participants, 7 patients (6.5%) sustained an acute myocardial infarction: 3 (6.0%) in the clopidogrel group and 4 (6.9%) in the placebo group (RR: 0.87, 95% CI: 0.20–3.7, $P = 0.85$). There were no in-patient deaths, intracranial hemorrhages or incidences of inotrope use. There was no difference in life-threatening major bleeding between treatment groups (7 [14%] clopidogrel and 6 [10%] placebo; RR: 1.35, 95% CI: 0.49–3.76; $P = 0.56$), although those who received clopidogrel had an increased risk of major nonlife-threatening bleeding (11 [22%] clopidogrel and 4 [7%] placebo, RR: 3.19, 95% CI: 1.1–9.4; $P = 0.024$; Fig. 4). Twenty (40%) patients receiving clopidogrel underwent red-cell transfusion compared with only 8 (14%) on placebo ($P = 0.0019$). Restricting analyses to transfusions administered in accordance with the SIGN guidelines, there remained an increased transfusion rate in the clopidogrel group (14 [28%] clopidogrel and 7 [12%] placebo; RR: 2.32, 95% CI: 1.02–5.29; $P = 0.037$). There was no difference in minor bleeding between the 2 groups (17 [34%] clopidogrel and 12 [21%] placebo; RR: 1.64, 95% CI: 0.87–3.10; $P = 0.12$). Five patients suffered gastrointestinal bleeding (hematemesis or melaena); 4 of whom were receiving placebo. Two patients received intraoperative protamine—1 in each intervention arm.

There were 2 reoperations for bleeding in the placebo group and 1 in the clopidogrel group. Although there was an increase in wound leak in those patients who received clopidogrel (13 [26%] vs. 3 [5%]; RR: 5.03, 95% CI: 1.52–16.6; $P = 0.0024$), there was no difference in incidence of wound infection at 3 months ($P = 0.80$). Clopidogrel therapy did not increase the length of operation ($P = 0.60$) or hospital stay ($P = 0.72$). Subgroup analysis of patients undergoing revascularization compared with amputation revealed no significant differences in clopidogrel versus placebo in terms of perioperative adverse cardiovascular events or bleeding outcomes (major life threatening, major nonlife threatening or minor). There were no incidences of early graft failure in either group.

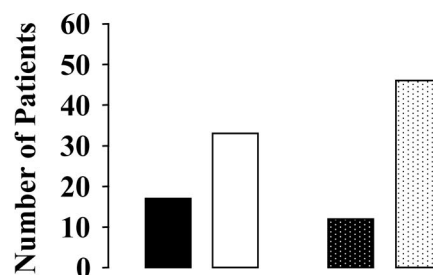
Major Life Threatening Bleeding



Major Non-life Threatening Bleeding



Minor Bleeding



Clopidogrel Placebo

FIGURE 4. Bleeding Outcomes. Major life-threatening (upper panel; RR: 1.35, 95% CI: 0.49–3.76, $P = 0.56$), major non-life-threatening (middle panel; RR: 3.19, 95% CI: 1.08–9.4, $P = 0.024$), and minor (RR: 1.64, 95% CI: 0.87–3.1, $P = 0.12$) bleeding (closed bars) in patients on clopidogrel (left-hand panels, nonstippled) or placebo (right-hand panels, stippled); χ^2 analysis.

DISCUSSION

We have conducted the first double-blind randomized controlled trial of perioperative dual antiplatelet therapy in patients undergoing surgery for critical limb ischemia. We demonstrate improvements in biomarkers of platelet activation and myocardial injury without causing unacceptable bleeding complications. These data form the first objective assessment of the risks and benefits of perioperative dual antiplatelet therapy in patients undergoing high-risk vascular procedures.

Peripheral arterial disease affects nearly 30 million people in Western Europe and North America. In up to 3-quarters of cases, patients have coexistent coronary artery disease and a 3-fold increased risk of cardiovascular events and death.²⁶ In a recent large

observational study ($n = 5460$), patients with peripheral arterial disease scheduled for open vascular surgery had a worse prognosis (2.4-fold increase in cardiovascular morbidity) than matched patients with severe myocardial ischemia referred for percutaneous coronary intervention.²⁷ Interestingly, the occurrence of perioperative cardiac complications following vascular surgery was associated with long-term cardiac death. There is therefore a clear unmet need to reduce cardiovascular events in patients with peripheral arterial disease, especially in the perioperative period.

In agreement with previous studies,^{2–5} we report a high incidence of perioperative myocardial infarction (6.5%) and troponin elevation (16.7%) in patients undergoing surgery for critical limb ischemia. We also found that postoperative elevations in troponin were associated with increased levels of postoperative platelet activation. However, we were surprised to find that markers of platelet activation fell postoperatively (both in clopidogrel and placebo groups) and that half of the troponin-positive events occurred before surgery. This occurred in the absence of renal dysfunction. This suggests that rather than surgery being an additional thrombotic stimulus, removal of ischemic tissue may actually reduce platelet activation in the majority of these patients. These findings highlight the prevalence of “silent” preoperative myocardial injury, and the important systemic prothrombotic consequences of critical limb ischemia, as well as the need for preoperative intervention.

This study aimed to explore a proof of concept. Preclinical studies of platelet activation in coronary patients have informed the design of large scale trials which have subsequently shaped clinical practice. These trials required several thousands of patients to demonstrate a small but significant clinical benefit from antiplatelet regimes. Despite suffering significant cardiovascular risk, there has been little study of platelet activation in high risk vascular surgical patients. The potential for adverse bleeding would seem greater for patients undergoing open surgery under antiplatelet therapy. Consequently, any large scale trial powered to examine clinical end points should be justified by “pilot” data suggesting that some cardiovascular benefit could be achieved without excessive bleeding.

Through the use of surrogate biomarkers, we have demonstrated the potential benefits of dual antiplatelet therapy in the peri-operative period. Clopidogrel reduced sensitive markers of platelet activation (Fig. 2) that are associated with increased clinical risk as well as the progression of atherothrombosis.^{11–17,28,29} Although clopidogrel did not have an overall effect on the number of peri-operative troponin-positive events (8 clopidogrel vs. 10 placebo; $P = 0.86$), half of the troponin elevations occurred preoperatively and prior to the administration of the study medication. Subsequent institution of clopidogrel therapy was associated with a marked reduction in troponin concentrations (Fig. 3). However, we readily acknowledge that our study was not primarily powered to assess cardiac troponin and clinical outcomes and whether these improvements in surrogate biomarkers translate into clinical benefit remains to be established.

All therapies have potential benefits and risks, and it is inevitable that antiplatelet therapies will be associated with increased bleeding complications. Although it may be regarded as potentially reversible, the importance of major bleeding must not be underestimated as it remains an independent predictor of adverse clinical outcome.^{30–32} Although vascular patients are at high risk of cardiovascular events, bleeding concerns are a major disincentive for the investigation of perioperative intensive antiplatelet regimes, and perhaps underlie the paucity of such data. Most published reports are observational,^{33,34} although randomized-controlled trials of dual antiplatelet therapy have been performed in patients undergoing carotid endarterectomy³⁵ and peripheral angioplasty,³⁶ and report no major increase in bleeding complications. However, there

have been no randomized-controlled trials of dual antiplatelet therapy in surgery for critical limb ischemia, where the potential for both perioperative bleeding and cardiac complications is greater. We have successfully delivered such a trial and confirmed that while bleeding is increased, there was no excess of life-threatening bleeds, reoperations, or wound infections. Our results are consistent those reported by the CURE trial,¹⁰ where those patients who continued clopidogrel therapy within 5 days of coronary artery bypass had a 2-fold increased relative risk of major bleeding. Arguably our pilot data suggests that the bleeding risks of dual antiplatelet therapy in the peri-operative period are modest, and perhaps often over estimated.

Increasingly patients are undergoing surgery for critical limb ischemia with a recent history of a cerebrovascular event, acute coronary syndrome, or percutaneous coronary intervention, and will be receiving intensive antiplatelet regimes. Their perioperative management must protect them from both coexisting pathology as well as the associated risks of surgery. Our study has shown that it is feasible to perform vascular surgery for critical limb ischemia, under dual antiplatelet therapy with an acceptable bleeding profile. Although the absolute clinical benefits of such a regimen need to be validated in a large-scale clinical trial, we believe that our study provides evidence for the beneficial role of perioperative antiplatelet agents in protecting these patients against cardiovascular complications.

Patients receiving epidural or spinal anesthesia were not recruited into the study due to the theoretical risk of epidural hematoma. We are aware that many vascular units aim for epidural or spinal anesthesia, thus precluding many patients from perioperative antiplatelet therapy. However, there is currently no level-one evidence for superior cardiovascular outcome with neuraxial blockade compared with general anesthesia. The main benefit lies in reducing respiratory complications associated with abdominal surgery.³⁷ Although many of the patients who were recruited smoked, none had significant chronic obstructive airway disease (based on lung function testing) and none were undergoing abdominal or emergency surgery. Use of both trial medication and general anesthesia was therefore deemed appropriate.

Persistent platelet reactivity despite antiplatelet therapy has been proposed as a risk factor for the recurrence of ischemic events following PCI. Recent mechanistic and clinical data suggest that higher loading and maintenance doses of clopidogrel may achieve a more rapid and greater degree of platelet inhibition that translates into improved clinical outcomes, but this is yet to be formally evaluated in an adequately powered randomized trial.³⁸ We administered a relatively high preoperative loading dose of clopidogrel (600 mg) to ensure efficacy of the intervention during surgery. It was hypothesized that if additional perioperative antiplatelet therapy was to be of any therapeutic advantage then this should be demonstrated with the largest degree of platelet inhibition. Previous studies have reported increased platelet activation^{29,39–42} and cardiovascular events occurring within the first 5 days following surgery. We therefore rationalized that clopidogrel therapy would be of most benefit when given preoperatively and continued in the immediate postoperative period. It is possible that we could still achieve atherothrombotic protection with reduced bleeding complications by administering lower doses of clopidogrel and this requires further clarification. However, given the relatively high incidence of troponin-positive events before surgery, we would recommend initiation of therapy prior to surgery.

In conclusion, we have demonstrated that perioperative dual antiplatelet therapy has beneficial effects on reducing biomarkers of atherothrombosis without increasing life-threatening bleeds in patients with critical limb ischemia. We propose that large-scale randomized controlled trials are needed to establish whether dual

antiplatelet therapy can improve clinical outcomes in high-risk patients undergoing vascular surgery.

ACKNOWLEDGMENTS

The authors thank all the clinical staff of the vascular unit, and in particular, Mr. R. T. A. Chalmers, Mr. S. C. A. Fraser, and Mr. Z. Raza; the Wellcome Trust Clinical Research Facility and the Clinical Biochemistry and Hematology Departments of the Royal Infirmary of Edinburgh.

REFERENCES

- Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:381–386.
- Mangano DT, Hollenberg M, Fegert G, et al. Perioperative myocardial ischaemia in patients undergoing non cardiac surgery—I: incidence and severity during the 4 day perioperative period. The Study of Perioperative Ischaemia (SPI) Research Group. *J Am Coll Cardiol*. 1991;17:843–850.
- Hobbs SD, Yapanis M, Burns PJ, et al. Peri-operative myocardial injury in patients undergoing surgery for critical limb ischaemia. *Eur J Vasc Endovasc Surg*. 2005;29:301–304.
- Kim LJ, Martinez EA, Faraday N, et al. Cardiac Troponin I predicts short-term mortality in vascular surgery patients. *Circulation*. 2002;106:2366–2371.
- Landesburg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischaemia with long term survival after major vascular surgery. *J Am Coll Cardiol*. 2003;42:1547–1554.
- Bertrand ME, Simoons ML, Fox KA, et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2002;23:1809–1840.
- CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;16:1329–1339.
- Bhatt DL, Fox KA, Hacke W, et al. CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717.
- Yusuf S, Zhao F, Mehta SR, et al. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.
- Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable Angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation*. 2004;110:1202–1208.
- Freedman JE, Loscalzo J. Platelet-monocyte aggregates: bridging thrombosis and inflammation. *Circulation*. 2002;105:2130–2132.
- McGregor L, Martin J, McGregor JL. Platelet-leucocyte aggregates and derived microparticles in inflammation, vascular remodeling and thrombosis. *Front Biosci*. 2006;11:830–837.
- Michelson AD, Barnard MR, Hechtman HB, et al. In vivo tracking of platelets: circulating degranulated platelets rapidly lose surface P-selectin but continue to circulate and function. *Proc Natl Acad Sci USA*. 1996;93:11877–11882.
- Huo Y, Schober A, Forlow SB, et al. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. *Nat Med*. 2003;9:61–67.
- Michelson AD, Barnard MR, Krueger LA, et al. Circulating monocyte-platelet aggregates are a more sensitive marker of in vivo platelet activation than platelet surface P-selectin: studies in baboons, human coronary intervention, and human acute myocardial infarction. *Circulation*. 2001;104:1533–1537.
- Harding SA, Josephs DH, Cruden NL, et al. Upregulation of the CD40/CD40 ligand dyad and platelet-monocyte aggregation in cigarette smokers. *Circulation*. 2004;109:1926–1929.
- Harding SA, Sommerfield AJ, Sarma J, et al. Increased CD40 ligand and platelet monocyte aggregates in patients with type 1 diabetes mellitus. *Atherosclerosis*. 2004;176:321–325.
- Cassar K, Bachoo P, Ford I, et al. Platelet activation is increased in peripheral arterial disease. *J Vasc Surg*. 2003;38:99–103.
- Sarma J, Laan CA, Alam S, et al. Increased platelet binding to circulating monocytes in acute coronary syndromes. *Circulation*. 2002;105:2166–2171.
- Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001;357:1191–1194.
- Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134:663–694.
- Harding SA, Din JN, Sarma J, et al. Flow cytometric analysis of circulating platelet monocyte aggregates in whole blood: methodological considerations. *Thromb Haemost*. 2007;98:451–456.
- Thygesen K, Alpert JS, White HD; The Joint European Society of Cardiology; American College of Cardiology; American Heart Association; World Heart Federation. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634–2653.
- Scottish Intercollegiate Guidelines Network. Perioperative blood transfusion for elective surgery. A national clinical guideline number 54. Edinburgh, United Kingdom: Scottish Intercollegiate Guidelines Network; 2001.
- Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.
- Hackam DG, Eikelboom JW. Antithrombotic treatment for peripheral arterial disease. *Heart*. 2007;93:303–308.
- Welten GM, Schouten O, Hoeks SE, et al. Long-term prognosis of patients with peripheral arterial disease: a comparison in patients with coronary artery disease. *J Am Coll Cardiol*. 2008;51:1588–1596.
- Furman MI, Barnard MR, Krueger LA, et al. Circulating monocyte-platelet aggregates are an early marker of acute myocardial infarction. *J Am Coll Cardiol*. 2001;38:1002–1006.
- Hayes PD, Box H, Tull S, et al. Patients' thromboembolic potential after carotid endarterectomy is related to the platelets' sensitivity to adenosine diphosphate. *J Vasc Surg*. 2003;38:1226–1231.
- Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114:774–782.
- Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24:1815–1823.
- Yang X, Alexander KP, Chen AY, et al. The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:1490–1495.
- Smout J, Stansby G. Current practice in the use of antiplatelet agents in the peri operative period by UK vascular surgeons. *Ann R Coll Surg Engl*. 2003;85:97–101.
- Assadian A, Senekowitsch C, Assadian O, et al. Antithrombotic strategies in vascular surgery: evidence and practice. *Eur J Vasc Endovasc Surg*. 2005;29:516–521.
- Payne AD, Jones CI, Hayes PD, et al. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. *Circulation*. 2004;109:1476–1481.
- Cassar K, Ford I, Greaves M, et al. Randomized clinical trial of the anti-platelet effects of aspirin-clopidogrel combination versus aspirin alone after lower limb angioplasty. *Br J Surg*. 2005;92:159–165.
- Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ*. 2000;321:1493.
- Mehta SR, Bassand JP, Chrolavicius S, et al. CURRENT-OASIS 7 Steering Committee. Design and rationale of CURRENT OASIS 7: a randomized, 2x2 factorial trial evaluating optimal dosing strategies for clopidogrel and aspirin in patients with ST and non-ST elevation acute coronary syndromes managed with an early invasive strategy. *Am Heart J*. 2008;156:1080–1088.
- Collins P, Ford I, Greaves M, et al. Surgical revascularization in patients with severe limb ischaemia induces a pro-thrombotic state. *Platelets*. 2006;17:311–317.
- Mohan IV, Mikhailidis DP, Stansby GP. Platelet activation in bypass surgery for critical limb ischaemia. *Vasc Endovasc Surg*. 2007;41:322–329.
- Samama CM, Thiry D, Elalamy I, et al. Perioperative activation of haemostasis in vascular surgery patients. *Anesthesiology*. 2001;94:74–78.
- Rajagopalan S, Ford I, Bachoo P, et al. Platelet activation, myocardial ischaemic events and post-operative non-response to aspirin in patients undergoing major vascular surgery. *J Thromb Haemost*. 2007;7:2028–2035.